UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OLIVER P. PEOPLES, LARA L. MADISON, and GJALT W. HUISMAN

Appeal No. 2005-1383
Application No. 09/364,847

ON BRIEF

ELLIS, GRIMES and GREEN, Administrative Patent Judge.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1-6, all the claims remaining in the application.

As a preliminary matter, we note the appellants' statement on page 4 of the Brief that the claims do not stand or fall together. 37 C.F.R. § 1.192(c)(7)(2003). The appellants contend that there are four groups of claims; Group I consisting of claim 1, Group II consisting of claim 2, Group III consisting of claims 3 and 4, and Group IV consisting of claims 5 and 6. Id. The appellants contend that they have provided "arguments for the separate patentability of groups 2 and 4." Id.

We point out that 37 C.F.R. § 1.192(c)(7)(2003) states, in relevant part, that for each ground of rejection, an appellant must "explain why the claims of the group are believed to be separately patentable. Merely pointing out differences in what the claims cover is not an argument as to why the claims are separately patentable."

If we were to follow the arguments on page 4 of the Brief, we would not consider the issues as they apply to claim 1, but only as they apply to claims 2 and 5 since these claims are representative of the two groups (groups 2 and 4) that the appellants state are separately patentable. However, because the examiner's Answer and the Brief are directed almost exclusively to independent claim 1, and correctly so, we would be remiss in our role as a reviewing tribunal if we did not focus our deliberations on the only independent claim on appeal.

With respect to the arguments on page 18 of the Brief, we find that the appellants have simply stated that the issues are different with regard to the subject matter of claims 2, 5 and 6, and that "no art has been cited to show" that said subject matter would have been obvious to one of ordinary skill in the art. The appellants do not provide any reasons as to why the referenced claims would not have been obvious based on the applied prior art. Thus, we find that the appellants have merely pointed out differences in the claims and have not stated why they are separately patentable. As indicated above, such action is improper. 37 C.F.R. § 1.192(c)(7)(2003). Nevertheless, we have included brief comments on claims 2, 5 and 6 in our deliberations below.

Claims 1, 2 and 4-6 are representative of the subject matter on appeal and read as follows:

1. A protein fusion having a formula selected from the group consisting of E1-L_n-E2 and E2-L_n-E1, wherein E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP:: coenzyme-A transferases, in which linker L_n is a peptide of n amino acids that links the carboxyl terminus of E1 to the amino terminus of E2 or the carboxyl terminus of E2 to the amino terminus of E1.

2. The fusion of claim 1 wherein E1 and E2 are selected from the group consisting of β-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; PHA synthase (phaC) and phasin (phaP); phaP and phaC; phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC.

4. The fusion of claim 1 wherein the linker is comprised of glycine-serine.

5. The fusion of claim 1 expressed in a plant.

6. The fusion of claim 1 expressed in bacteria.

The references relied upon by the examiner are:

Peoples et al. (Peoples) 5,245,023 Sep. 14, 1993

Argos, "An Investigation of Oligopeptides Linking Domains in Protein Tertiary Structures and Possible Candidates for General Gene Fusion," J. Mol. Biol., Vol. 211, pp. 943-958 (1990)

Bülow et al. (Bülow), "Multienzyme Systems Obtained by Gene Fusion," TIBTECH, Vol. 9, pp. 226-231(1991)

The claims stand rejected as follows:

I. Claims 1-6 stand rejected under 35 U.S.C § 112, first paragraph, as being based on a specification which fails to provide an adequate written description of the invention.

II. Claims 1-3, 5 and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Peoples and Bülow.

III. Claim 4 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Peoples, Bülow and Argos.

We reverse Rejection I, but affirm Rejections II and III.

Background

Poly[(R)-3-hydroxyalkanoate] polymers (PHAs) "are biodegradable and biocompatible thermoplastic materials with a broad range of industrial and biomedical applications." Specification, p. 1, lines 14-16. According to the specification, PHAs are divided into two groups depending on "the lengths of their side chains and their biosynthetic pathways." Id., lines 22-24. "Those with short side chains, such as polyhydroxybutyrate (PHB), a homopolymer of R-3-hydroxybutyric acid units, are semi-crystalline thermoplastics, whereas PHAs with long side chains are more elastomeric." Id., lines 24-27.

The specification further discloses that "[b]iosynthesis of the short side-chain PHAs such as PHB and PHBV proceeds through a sequence of three enzyme catalyzed reactions from the central metabolite acetyl-CoA [specification, p. 1, lines 28-30]"; whereas, "[l]ong side chain PHAs are produced from intermediates of fatty acid β-oxidation or fatty acid biosynthesis pathways [id., p. 2, lines 12-13]."

Since "[i]t is desirable for economic reasons to be able to produce [the aforementioned] polymers [PHAs] in transgenic crop species [specification, p. 3, lines 5-6]" or microorganisms, the specification discloses methods of making fusion proteins which comprise the two "catalytically active enzymes which act on a substrate in successive reactions in a polyhydroxyalkanoate [PHA] biosynthetic pathway" [claim 1] which are "selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly (3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases [claim 1]," wherein the enzymes are said to be separated by a peptide linker.

Discussion

I. Written description

The examiner acknowledges that the specification teaches the structure of several different fusion proteins. Answer, p. 5. The examiner further acknowledges that "the specification provides references (pages 8-11) that are asserted to disclose other naturally occurring nucleic acid sequences of genes from microorganisms encoding the enzymes recited in claims 1 and 2." Id. However, the examiner argues that "the genera of enzymes recited in the claims are not [] limited to those enzymes encoded by the naturally occurring genes disclosed in the specification." Id. The examiner further argues that "the genera of enzymes as recited in claims 1 and 2 encompass species from any source, including species that have not been described in the specification, and further encompass mutant enzymes . . . that have not been disclosed in the specification." Id. According to the examiner,

> . . . with the recited genera of enzymes comprising the fusion protein, the functional definition of the genus does not provide structural information commonly possessed by all members of the genus, which distinguish the enzyme species within the genus such that a skilled artisan can visualize or recognize the identity of all species of recited enzymes from any source. Besides the disclosed species, the specification fails to describe any other representative species of naturally occurring or mutant enzymes by any identifying characteristics or properties other than the functionality of being a fusion of the individual enzyme subunits as recited in claims 1 and 2 [Answer, p. 6].

The examiner contends that "the structures of all species encompassed by the recited genera of enzymes is [sic, are] unpredictable." Id.

It is well established that the purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims does not overreach the scope of the inventor's contribution to the field as far as described in the patent specification." Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000). To that end, to satisfy the written description requirement, the inventor "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). "One shows that one is 'in possession' of the invention by describing the invention, with all its claimed limitations . . ."). Lockwood v. American Airlines, 107 F.3d 1563, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

We point out that it is not necessary for the specification to describe the claimed invention ipsissimis verbis; all that is required is that it reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. Union Oil of California v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); Vas-Cath Inc. v. Mahurkar, 935 F.2d at

1563-64, 19 USPQ2d at 1117; In re Gosteli, 872 F.2d 1008,1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); In re Edwards, 568 F.2d 1349, 1351-52,196 USPQ 465, 467 (CCPA 1978).

With respect to the written description of inventions involving a chemical genus, the Federal Circuit has stated that "a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lily and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1404, quoting Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Moreover, a "functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art." In re Wallach, 378 F.3d 1330, 1334, 71 USPQ2d 1939, 1943 (Fed. Cir 2004); see also, University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 925, 69 USP2d 1886, 1893 (Fed. Cir. 2004); Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

We appreciate the examiner's concerns with respect to the claims being directed to a genus of enzymes which are described by their function; however, we find that, in the case before us, the specification reasonably conveys to one skilled in the art that the appellants were in possession of the invention at the time the application was filed. Union Oil of California v. Atlantic Richfield Co., 208 F.3d at 997; Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64; In re Gosteli, 872 F.2d at 1012; In re Edwards, 568 F.2d at 1351-52. Here, it appears that the examiner has studied the appellants' disclosure and formulated a conclusion as to what he (the examiner) regards as the broadest possible invention, and then determined that the appellants' claims are

directed to an invention which is broader than that which is described in the specification. This analysis is improper. We remind the examiner that written description is determined from the perspective of what the specification conveys to one skilled in the art. In re GPAC Inc., 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64. Thus, the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." LizardTech Inc., v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1344-45, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

The present invention is not about novel enzymes; it is about making fusion proteins (or protein fusions) which comprise known enzymes. In this regard, we direct attention to the examiner's acquiescence to the appellants' argument that the proteins, and genes which encode them, are known and publicly available. Answer, pp. 2-3; Brief, pp. 6-7. We point out that the examiner appears to have agreed with the appellants that pages 8-10 of the specification, pages 4-8 of the appellants' response mailed December 27, 2002 (entered January 2, 2003), and the Medline database[1] demonstrate that given the homology between both the amino acid and nucleotide sequences of the enzymes in each of the claimed classes, one skilled in the art could readily obtain the enzymes from various species. Answer, p. 3; Brief, p. 7. That is, in

[1] It is not clear to us on what "Medline database" the appellants are relying. We find no exhibits in the file which support this argument. Accordingly, at least with respect to the "Medline database," we find that the appellants are relying only on argument of counsel. We point out that argument of counsel cannot take the place of objective evidence. In re Payne, 606 F.2d 303, 315, 203 USPQ 245, 256 (CCPA 1979); In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1971). Thus, we accord the argument in this regard little, or no, evidentiary weight.

withdrawing the enablement rejection, the examiner appears to have agreed with the appellants that one skilled in the art would readily recognize the PHA biosynthetic enzymes within each of the claimed classes of enzymes based on amino acid sequences known in the art. Id., p. 8. We recognize that these arguments were made in response to the enablement rejection, and that our appellate reviewing court has consistently held that enablement and description are two separate requirements.[2] University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d at 921; Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d at 963. However, we point out that "a recitation of how to make and use an invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention and vice versa." LizardTech Inc., v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1343, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005). Having agreed with the appellants that there was no problem with the scope of the claims with respect to enablement, and that one skilled in the art could readily obtain or construct the enzymes encompassed by the claims, the examiner is in a poor position to argue that the specification fails to provides an

[2] We point out that the comingling of the enablement and written description issues is reflected in the examiner's arguments. That is, the examiner argues that the specification fails to provide an adequate written description of the claimed invention because "the structures of all species encompassed by the recited genera of enzymes is [sic, are] unpredictable." Answer, p. 6. Unpredictability is a factor which is considered in determining whether the specification would have enabled one skilled in the art to make and use the claimed invention without undue experimentation. See, In re Wands, 858 F.2d 731, 736-37, 8 USPQ2d 1400, 1404 Fed. Cir. 1988). Thus, the examiner's arguments in this regard are not appropriate in the context of the written description rejection.

adequate written description of said invention. That is, if one skilled in the art is able to make and use the enzymes within the scope of the claims based on the teachings of the specification and what was known in the art at the time of the invention (enablement), as indicated by the examiner, then it reasonably follows that such person would understand or recognize said enzymes from the same information source(s) (written description).

We agree with the examiner that in certain instances, such as those presented by the facts in the University of California v. Eli Lily and Co., 119 F.3d at 1568, the court has held that nucleotide sequences are such complex chemical compounds that one skilled in the art cannot envision the genus of mammalian nucleotide sequences of a particular gene simply by knowing the nucleotide sequence of a single species. However, a claim is not unpatentable simply because the "embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." LizardTech Inc., v. Earth Resource Mapping, Inc., 424 F.3d at 1343; see also, Union Oil Co. v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000). As discussed above, a patent application is written for a person of skill in the art. In re GPAC Inc., 57 F.3d at 1579; Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64. Since the evidence of record demonstrates that the claimed classes of enzymes were well known in the art (pages 8-10 of the specification; pages 4-8 of the appellants' response (Jan. 2, 2003)), we find that one skilled in the art would readily recognize the enzymes involved in the PHA biosynthetic pathway even if they are derived from different microorganisms and there are minor differences in the amino acid sequences. Accordingly, we find that the appellants were in possession of the claimed

invention at the time the application was filed. Vas-Cath Inc. v. Mahurkar, 935 F.2d at 1563-64.

In view of the foregoing, Rejection I is reversed.

II. Obviousness over Peoples and Bülow

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

Here, the examiner argues that Peoples discloses "the isolation and nucleotide sequence of genes encoding beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase from Zoogloea ramigera and Alcaligenes eutrophus (columns 6-14 and Figures 1-4)." Answer, p. 7. The examiner further argues that Peoples discloses (i) that "co-expression of beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase genes in E. coli results in the formation and accumulation of PHB (e.g., column 19, lines 36-40 and column 22, lines 18-21)"; (ii) "beta-ketothiolase, acetoacetyl-CoA reductase, and PHB polymerase can be co-expressed in plants"; (iii) "methods of engineering plant cells for expression of the enzymes for production of PHB"; and (iv) "a representative example of a PHB polymerase-PHA polymerase fusion enzyme (column 23,

lines 16-18)." Id. The examiner states that Peoples does "not teach a fusion of enzymes catalyzing successive enzymatic reactions [emphasis added]." To that end, the examiner relies on the teachings of Bülow that the (i) "preparation of a bifunctional enzyme can be accomplished by joining the genes of two enzymes by removing the translational stop signal at the 3'-end of the first gene and ligating the ATG-start codon of the second gene in-frame with the first gene"; (ii) "the enzyme selected to be at the N-terminal end [of a bifunctional enzyme] is arbitrary and that the native tertiary structure of the fused enzymes remains almost intact"; (iii) "if the entire primary sequences of the [] native enzymes are maintained in [a] fusion, the enzymes usually retain most of their native specific activities despite being fused together;" and (iv) "a linker peptide of two to ten amino acids separating the fused native enzymes [of a bifunctional enzyme] is optimal." Id., p. 8.

The examiner concludes that

> . . . it would have been obvious to one of ordinary skill in the art to combine the teachings of Peoples [] and Bulow [] for a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids expressed in E. coli or a plant. One would have been motivated to make a beta-ketothiolase and acetoacetyl-CoA reductase or acetoacetyl-CoA reductase and PHB polymerase fusion protein having a linker of between two and ten amino acids for expression in E. coli or a plant because of the teachings of Peoples [] who teach PHB is a commercially useful biopolymer that can be expressed in bacteria or plants as described above and Bulow [] who teach the advantages of fusion proteins, particularly those catalyzing sequential enzymatic reactions and that a linker of two to ten amino acids separating the native enzymes is optimal as described above [Answer, pp. 8-9].

In response, the appellants argue that Peoples "teaches the construction of polymerase fusions for the purpose of 'altering the enzyme's specificity to create novel polymerases' (see column 23, lines 14-24)." Brief, p. 16. The appellants further argue

that because the fusion protein taught by Peoples comprises the genes encoding PHB and PHA polymerase, said protein would not catalyze successive reactions in a PHA pathway, "but alternative reactions- i.e., either addition of short chain or long chain substrate" [emphasis omitted]. Id. With respect to the teachings of Bülow, the appellants contend that they are prophetic and, thus, do not provide an expectation that a fusion protein comprising enzymes which catalyze successive reactions would be successful. Id., p. 16. We find these arguments unpersuasive.

First, we find that the appellants' arguments in the Brief are primarily focused on the shortcomings of the individual references and are not directed to the combined teachings of Peoples and Bülow. We point out that the references were relied on in combination and that the appellant cannot demonstrate nonobviousness by attacking the references individually. In re Betz, 418 F.2d 942, 947, 163 USPQ 691, 695 (CCPA 1969); In re Young, 403 F.2d 754, 757, 159 USPQ 725, 728 (CCPA 1968).

Second, we agree with the examiner that Peoples, in combination with Bülow, would have suggested to one of ordinary skill in the art the invention set forth in representative claim 1.[3] In this regard, we find that Peoples discloses DNA sequences which encode two catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway, and plasmids which comprise said DNA sequences. For example, Peoples discloses constructing plasmids which express two

[3] Although Peoples assays the isolated β-ketothiolase and acetoacetyl-CoA reductase genes disclosed therein for their ability to produce PHB (see, e.g., Tables 2 and 3), these enzymes are the same as those involved in the production of PHA. See, pages 1-2 of the specification. In fact, the specification discloses the isolation of the same β-ketothiolase and acetoacetyl-CoA reductase genes from A. eutrophus as is taught by Peoples (page 18, lines 17-25), and performs the same assays for PHB activity (see, e.g., Table I, page 22) with the enzymes said genes encode.

catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway and which are under the control of a single promoter. Attention is directed to column 22, lines 26-30, which states that plasmids can be constructed which express the β-ketothiolase and acetoacetyl-CoA reductase genes from A. eutrophus. Attention is further directed to Figure 3 which shows an isolated 2 kb DNA fragment from A. eutrophus which encodes the β-ketothiolase (nucleotides 40-1219) and the acetoacetyl-CoA reductase (nucleotides 1296 to 2034) genes. See also columns 11-12, which disclose two plasmids, pZT1 and pZT2, which encode the β-ketothiolase and acetoacetyl-CoA reductase genes derived from Z. ramigera. The only difference between the plasmids (and enzymes which they encode) taught by Peoples and the present invention is that the catalytically active enzymes disclosed in the patent are present in tandem (fused, if you will) on a single DNA fragment. Thus, when said DNA is expressed (due to the processing which occurs within the microorganism) two separate enzymes are produced, rather than a fused protein comprising both.[4]

Peoples further discloses the construction of plasmids which encode either (i) a promoter derived from A. eutrophus (the PHB polymerase or phbC promoter), the PHA polymerase structural gene (derived from P. oleovorans), and the ORF2 region of the PHA polymerase gene (ORF2 is said to be a protein cotranscribed with the PHA

[4] We point out that dependent claim 3, states that the linker L_n can comprise between zero and 50 amino acids. Thus, because independent claim 1 contains all of the limitations present in dependent claim 3, we find that the protein fusion recited in claim 1 need not have any amino acids between the two catalytically active enzymes E1 and E2.

polymerase gene which is involved in PHA biosynthesis, col. 22, lines 12-15)(see, pAeP1 and pLAP1); or (ii) a promoter derived from A. eutrophus (the PHB polymerase or phbC promoter), the PHA polymerase structural gene (derived from P. oleovorans) and the ORF2 and ORF3 regions of the PHA polymerase gene (see, pAeP2 and pLAP2, and Figure 3). Accordingly, we find that this section of the patent also describes fusion plasmids encoding catalytically active enzymes which act on a substrate in successive reactions in a PHA biosynthetic pathway (viz., pAeP1 and pLAP1).

In addition to the cloned and characterized genes discussed above, Peoples suggests a protein fusion comprising two catalytically active enzymes in the PHA and PHB biosynthetic pathways; i.e., a fusion of the PHA and PHB polymerase structural genes. Peoples, col. 23, lines 20-22. Peoples does not suggest a protein fusion of the catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway discussed above; this suggestion comes from Bülow.

To that end we find, and the appellants do not disagree, that Bülow suggests the construction of fusion proteins comprising two or more enzymes involved in sequential reactions. Bülow discloses that the use of enzymes catalyzing sequential reactions "is a feature of many biotechnological production processes and biochemical analyses." Bülow, p. 226, col. 1, first sentence; see also, the entire para. Bülow further discloses the importance of "generating physical proximity between the enzymes (e.g. by co-immobilization of two or more enzymes to a matrix or support) [as it] often provides . . . highly attractive properties [such as] stabilization and re-usability of the biocatalyst, [as well as] improv[ing] the kinetic characteristics of the reaction." Id., para. bridging

pp. 226-27. As pointed out by the examiner, Bülow still further discloses different methods of "creating proximity between the enzymes" (p. 227, col. 1, first complete para.) which include gene fusions which "maintain the monomeric character of the native enzymes" (id., col. 2, first complete para.) by "joining the structural genes of two enzymes: the translational stop signal at the 3' end of the first gene is removed and ligated in-frame to the ATG start codon of the second gene" (id., col. 1, para. 3). Bülow still further discloses that through experience, it has "found that fairly short linkers (two to ten amino acid residues) [between the fused enzymes] are optimal." Id., p. 230, col. 1, first complete para.; see also, Figure 1c and Figure 3. Bülow exemplifies several fusion proteins consisting of catalytically active enzymes which act on substrate in successive reactions. See, the β-galactosidase-galactokinase fusion protein (pp. 227-228), the β-galactosidase-galactose dehydrogenase fusion protein (p. 228, cols. 1-2), and the bovine P-450s and yeast reductase fusion protein (p. 229, col. 2). Not only does Bülow exemplify several fusion proteins, but the publication reports that "[o]ver the past few years a variety of artificial bifunctional enzymes have been prepared by gene fusion in vitro." Id., p. 227, col. 2, last para.

Accordingly, in view of the teachings of Peoples with respect to the construction of (i) plasmids comprising two catalytically active enzymes in the PHA biosynthetic pathway which act on a substrate in successive reactions (see, e.g., col. 22, lines 26-30; Figure 3); and (ii) protein fusions comprising catalytically active enzymes involved in the PHA biosynthetic pathway (col. 23, lines 14-24), and the teachings of Bülow as to the construction of bifunctional enzymes comprising two enzymes involved in successive reactions, the advantages of said constructions, and that said

constructions are well known and widely used in the art, it would have been obvious to one of ordinary skill in the art to construct a protein fusion comprising two catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway. Although, as discussed in footnote 4, above, we find that the protein fusion of representative claim 1 does not require the presence of a peptide linker (when L_n is zero), we point out that given the teachings of Bülow that the use of short linkers two to ten amino acids in length produces optimal results in bifunctional enzymes, it would have been further obvious to said persons to include a linker peptide in said fusion.

We disagree with the appellants that the teachings of Bülow do not provide a reasonable expectation of success. As discussed above, Bülow discloses that (i) as long as "the entire primary sequences of the native enzymes are maintained in the fusion enzymes, the enzymes usually retain most of their native specific activities despite being fused together" (p. 230, col. 1, para. 1); and (ii) "[o]ver the past few years a variety of artificial bifunctional enzymes have been prepared by gene fusion in vitro" (p. 227, col. 2, last para.). In our view, these teachings demonstrate that the technique of combining enzymes which act on substrate in successive reactions is widely applicable. Moreover, we point out that representative claim 1 is not directed to a protein fusion consisting of specific catalytically active enzymes but, rather, it is directed to classes of enzymes involved in a PHA biosynthetic pathway. Accordingly, given the breadth of the claim, it is not clear that appellants' argument addresses a particular limitation present therein. Nevertheless, we find that those skilled in the art would have reasonably expected the technique taught by Bülow to be equally successful using the claimed classes of enzymes recited in claim 1. Obviousness does not require absolute

predictability, only a reasonable expectation of success. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

As to the appellants' contention that the art does not render the specific enzymes of claim 2 obvious, we direct attention to the teachings of Peoples. As discussed above, Peoples discloses that the β-ketothiolase gene is just upstream from acyl-CoA reductase gene in the bacterial genome (Figure 3, col. 11, line 61-col. 12, line 51). In addition, Peoples discloses that recombinant plasmids which comprise a β-ketothiolase gene in the upstream position from an acyl-CoA reductase gene encode catalytically active enzymes; i.e., enzymes having PHB polymerase activity. See pZT1 and pZT2 in col. 12, lines 26-51. Accordingly, given the teachings of Peoples with respect to DNA sequences and recombinant plasmids comprising a β-ketothiolase gene (phbA) and an acyl-CoA reductase gene (phbB), linked in a tandem arrangement, wherein said genes encode catalytically active enzymes which act on substrate in successive reactions in a PHA biosynthetic pathway, and the teachings of Bülow with respect to the construction of bifunctional enzymes comprising two enzymes which act on a substrate in succession, we hold that it would have been obvious to one of ordinary skill in the art to construct a protein fusion consisting of β-ketothiolase (phbA) and acyl-CoA reductase (phbB).[5]

Finally, we find the appellants' argument that "no art has been cited to show that the fusions of claims 5 and 6, in a host bacterium or plant cell would [have been] obvious to one of ordinary skill in the art" (Brief, p. 18), to be misdirected.

[5] We point out that like claim 1, claim 2 does not require that the protein fusion have a peptide linker between the two catalytically-active enzymes.

First, we point out that claims 5 and 6 are in a product-by-process format. The appellants are advised that an invention defined in this manner is a product and not a process. In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). Thus, it is the patentability of the product which must be considered. In the case before us, we do not find, and the appellants have not pointed out, any characteristics which distinguish the protein fusion recited in claims 5 and 6 from that which is recited in claim 1. That is, the fusion protein of claim 1 does not automatically change when it is expressed in a plant cell or in bacteria. Thus, the reasons for our finding the fusion protein of claim 1 unpatentable over the teachings of Peoples and Bülow apply with equal force to claims 5 and 6 because they are directed to the same composition.

Second, even if we assume arguendo, that claims 5 and 6 are directed to a method of expressing the fusion protein in a plant cell or a bacterium, we would find the appellants' argument unconvincing. We point out that Bülow discloses the expression of the recombinant bifunctional enzymes in bacteria (E. coli). More importantly, both the specification (p. 1, lines 13-14) and Peoples discloses that PHA is naturally produced in bacteria (e.g., col. 2, lines 50-52). Peoples further discloses the isolation and expression of numerous genes which encode catalytically active enzymes involved in the PHA biosynthetic pathway in bacteria (e.g., col. 3, lines 38-41, lines 50-64; col. 12, lines 19-51; col. 14, lines 20-33; col. 16, lines 16-56; col. 19, lines 23-60; Tables 2 and 3). Peoples still further discloses that the genes encoding the thiolase, reductase and/or polymerase for PHA can be expressed in plants to produce the desired product (e.g., col. 3, lines 38-41, lines 44-49 and lines 63-66; col. 26, lines 42-46). Thus, assuming arguendo that claims 5 and 6 were directed to the expression of the protein

fusion set forth in claim 1 in bacteria and plants, we would have held that the applied prior art would have suggested said expression to one of ordinary skill in the art.

Accordingly, in view of the foregoing Rejection II is affirmed.

III. Obviousness in further view of Argos

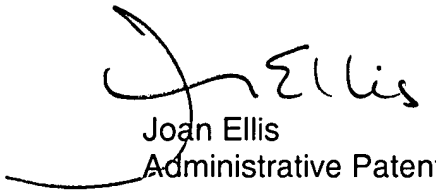
The examiner relies on Peoples and Bülow for the reasons set forth above. In addition, the examiner relies on the teachings of Argos with respect to "the advantages of using an oligopeptide linker comprising glycine, serine, and threonine." Answer, p. 9.

Because this rejection is based on the teachings of Peoples and Bülow, the appellants simply rely on their arguments above. Brief, p. 17. Indeed, the appellants' only argument is that this rejection is moot.

Accordingly, since it is not contested, Rejection III is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED



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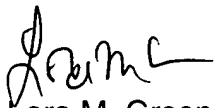
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